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Specifically, it is asserted in the Office Action that the presently claimed arrays and methods of creating them are not limited to any specific length of constant and random regions nor any minimum number of probes and thus the claims read on the use of as few as two probes of any length having a variable region of a single nucleotide. It is alleged that because Khrapko teaches the use of a probe array comprising a constant region attached to a solid phase and a variable region of 1-2 nucleotides, and Drmanac teaches the use of probes of 11-20 nucleotides and 3 random positions, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a variable region of any size for the expected benefit of detecting as many target sequences as possible. The bigger the array of variable sequences, the more targets that can be identified and the more useful the array will be.

It is further asserted in the Office Action that with respect to claims that recite various specific types of labels and solid phases, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use any labels or solid phase because, as taught by Khrapko (*e.g.*, p. 385, section entitled "CSH"), only the interaction between the probe and target sequence is critical to the function of the method. Thus, it is alleged that the ordinary artisan would have reasonably expected any labels or solid phase material to function in the claimed invention.

It is also asserted that although some of the claims differ from Khrapko in the recitation of identification and detection steps, Drmanac teaches a method of nucleic acid detection or identification comprising contacting a nucleic acid with a sample bound to a solid phase. It is concluded that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the materials of Khrapko in the method of Drmanac because the methods of Drmanac increase the discrimination of detection methods, an advantage explicitly taught as desirable in Drmanac.

Reconsideration and withdrawal of this rejection is respectfully requested.

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The Claims

Claims 1-5, 65-69 and 111-113 are directed to methods of creating an array of probes which include steps of synthesizing a first set of nucleic acids containing a constant sequence and a random sequence and hybridizing the first set of nucleic acids with a second set of nucleic acids each containing a sequence complementary to the constant sequence of the first nucleic acid. Claims 1, 2, 5 and 65-69 specify that the double-stranded region comprises the constant sequence. Claims 111 and 112 specify that the random sequence is of length R. Claims 113, 3 and 4 specify that the constant sequence is of length C at a 3' terminus and that the random sequence is of length R at a 5' terminus.

Claims 70-79, 114 and 115 are directed to an array of nucleic acid probes that have a double-stranded portion and a single-stranded portion containing a random nucleotide sequence. Claims 70-79 and 115 specify that the random nucleotide sequence is of length R. Claim 114 specifies that the double-stranded portion comprises a constant sequence.

Claims 89-94 and 116 are directed to a solid support comprising an array of nucleic acid probes that have a double-stranded portion and a single-stranded portion containing a random nucleotide sequence. Claims 89-94 specify that the random nucleotide sequence of the probes is of length R. Claim 116 specifies that the double-stranded portion of the probes comprises a constant sequence.

Claims 95-110 and 117-120 are directed to methods of sequencing a target nucleic acid including steps of hybridizing target nucleic acid that is at least partly single-stranded to an array of nucleic acid probes that have a double-stranded portion and a single-stranded portion containing a random nucleotide sequence and either detecting the hybridized target nucleic acid for sequencing thereof or determining a hybridization pattern whereby the target nucleic acid is sequenced by analyzing the hybridization pattern. Claims 117

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and 119 specify that the random nucleotide sequence is of length R. Claims 118 and 120 specify that the double-stranded portion comprises a constant sequence.

Claims 80-88 and 121-122 are directed to methods of detecting a target nucleic acid in a biological sample including steps of contacting an array of probes that have a double-stranded portion and a single-stranded portion containing a random nucleotide sequence and identifying hybrids to detect the target nucleic acid. Claim 121 specifies that the random nucleotide sequence is of length R. Claim 122 specifies that the double-stranded portion comprises a constant sequence.

Cited Art

Khrapko *et al.*

Khrapko *et al.* describes a technique of DNA sequencing by hybridization with an oligonucleotide matrix (SHOM) and experiments to test the method on a short (17 nucleotides) DNA fragment prior to a full-scale trial of the method. The efficiency of SHOM is stated to depend on the ability to sort out effectively perfect duplexes from imperfect duplexes (i.e., containing base pair mismatches) which can be achieved by comparing the temperature-dependent dissociation curves of the duplexes formed by DNA and each of the immobilized oligonucleotides, with standard dissociation curves for perfect oligonucleotide duplexes.

In experiments described in Khrapko *et al.* to test SHOM, single-stranded 8-mers were immobilized to a polyacrylamide-covered glass plate. Four single-stranded 17-mers differing by a single base substitution were separately hybridized to the immobilized 8-mers, each of which was complementary to a portion of one of the 17-mers. The hybridizations would thus form perfect as well as imperfect (single mismatches) duplexes. The duplexes were subjected to a series of washes at increasing temperatures and thermal dissociation curves were generated and compared to distinguish perfect from imperfect

hybridizations.

It is suggested in Khrapko *et al.* that additional continuous stacking hybridization (CSH), referred to as hybridization of DNA with immobilized octanucleotides **in the presence of** labeled selected pentanucleotides to form a continuously stacked perfect duplex of 13 base pairs, could increase the fidelity of SHOM (emphasis added, see page 376, first full paragraph in left column). Additional experiments reviewed in Khrapko *et al.* include a "numerical" experiment to estimate the efficiency of CSH. In the description of CSH (p. 385, first full paragraph in left column), Khrapko *et al.* state that it is based on the fact that when two oligonucleotides are **simultaneously** hybridized to a longer one, the two duplexes are mutually stabilized if they are positioned side-by-side due to a stacking contact between them. Figure 8 of Khrapko *et al.* is said to illustrate this effect.

Figure 8 of Khrapko *et al.* shows dissociation curves for four different hybridization products. In the four hybridization reactions, a ³²P-labeled 5-mer and the "test" 17-mer were simultaneously hybridized with an immobilized oligonucleotide (i.e, four different oligonucleotides were immobilized on matrix: 3 different 8-mers and one 7-mer). The hybridization products were subjected to washes of increasing temperature in order to generate the dissociation curves shown. It is concluded that (1) the 5-mer makes a stable duplex when hybridized to a complementary 17-mer together with immobilized 8-mer due to the continuous stacking contact and (2) the stability of the 5-mer duplex decreases if stacking is disrupted by nucleotide displacement, gap or terminal mismatch.

Drmanac *et al.*

Drmanac *et al.* describes experiments designed to investigate possible DNA hybridization conditions that may permit discrimination between perfectly matched duplexes and duplexes with a single mismatch. In these experiments, single-stranded DNA was spotted on a membrane and then hybridized with an

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oligomer probe end-labeled with ^{32}P . Autoradiographs of the filters were made and, for discrimination measurements, the dots were excised from the dried filters after radiography, and the radioactivity of the dots was measured using liquid scintillation counting methods. Preliminary characterization of the thermal stability of short oligonucleotide hybrids was determined on prototype fully matched hybrids or hybrids containing one mismatch: (1) TGCTCATG or GCTCAT hybridized to dot blots containing NCATGAGCANN and (2) GCTCAT hybridized to dot blots of NNCATGAGTTN.

In addition to experiments with model oligonucleotides, an M13 vector and derivative thereof (i.e., vector IF which is an M13 recombinant with a 921-bp human interferon gene insert that carries a single perfectly matched target) were used as a system for a practical demonstration of hybridization to short oligonucleotide probes of 6, 7 or 8 nucleotides. It is concluded in Drmanac *et al.* that using low-temperature conditions, sufficient difference in hybridization signal was obtained between the dot containing the perfect and mismatched targets and the dot containing only the mismatched targets.

To allegedly show the general utility of the proposed conditions, Drmanac *et al.* examined hybridization of 4 heptamers, 10 octamers and 14 additional probes up to 12 nucleotides long in the M13 system. To allegedly show the utility of the method in fingerprinting unknown clones for the presence of a short sequence, three probes 8 nucleotides long were tested on a collection of 51 plasmid DNA dots made from a library in Bluescript vector.

Relevant law

In order to establish *prima facie* obviousness, the prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). The mere fact that prior art may be modified as suggested by the Examiner does not make the modification obvious **unless the prior art suggested the desirability of the**

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modification (*In re Gordon*, 733 F.2d at 902, 221 USPQ at 1127). In addition, the combination of references or the cited reference with the knowledge of those of ordinary skill in the art must result in the claimed subject matter. Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.* 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The methods of claims 1-5, 65-69 and 111-113 are not taught or suggested by the cited references

Claims directed to methods of creating an array of probes (claims 1-5, 65-69 and 111-113) specify that a first set of nucleic acids containing a constant sequence and a random sequence is hybridized with a second set of nucleic acids each containing a sequence complementary to the constant sequence of the first nucleic acid to generate an array of probes having a double-stranded region and a single-stranded region containing the random sequence. Claims 1, 2, 5 and 65-69 further specify that the double-stranded region comprises the constant sequence. Claims 111 and 112 further specify that the random sequence is of length R. Claims 113, 3 and 4 further specify that the constant sequence is of length C at a 3' terminus and that the random sequence is of length R at a 5' terminus. As described in detail in the specification, the arrays created by the claimed methods may be used in nucleic acid analyses including sequencing, purification, detection and identification processes. Thus, the

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arrays can be used in the analysis of target nucleic acids which hybridize to the probes. As stated in the specification, a principle advantage of the probes is in their structure (the presence of a double-stranded and single-stranded region containing a random sequence). Hybridization of target nucleic acids to single-stranded regions of the probes is encouraged due to the favorable thermodynamic conditions established by the existence of the double-stranded region in the probe.

Khrapko *et al.* does not teach or suggest the methods of claims 1-5, 65-69 and 111-113. As discussed above, Khrapko *et al.* describes a technique, referred to as sequencing by hybridization with an oligonucleotide matrix (SHOM) and experiments to (1) test the method using a 17-nucleotide DNA fragment and (2) illustrate the effect of continuous stacking hybridization (CSH). These experiments were conducted not to generate an array of probes having a double-stranded region and a single-stranded region containing a random sequence, but instead to simulate, on a small scale, sequencing by hybridization of a target DNA fragment to a matrix of **single-stranded** probes. The resulting hybrids in these experiments represent those formed after a prototype target nucleic acid to be sequenced hybridizes to a single-stranded probe.

Specifically, in the test and illustrative experiments described in Khrapko *et al.*, 17-mers were hybridized to matrices containing 8-mers and/or 7-mers. None of the resulting hybridized matrices described in Khrapko *et al.* contains an array of probes that is generated from the claimed methods. For example, Figure 8 of Khrapko *et al.* depicts the products resulting from hybridization of a 17-mer to four immobilized oligonucleotides (i.e., three different 8-mers and a 7-mer) in the presence of a 5-mer. The resulting hybridization matrix does not contain probes which contain a double-stranded region and a single-stranded region **containing a random sequence** as are made, and specified, in all of the claimed methods for creating an array of probes. The only single-stranded regions of the hybrids depicted in Figure 8 of Khrapko *et al.* are 7 "TG"

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dinucleotides and one "ATG" trinucleotide extending 5' and 3' of the double-stranded portions of the hybrids, which are not random sequences.

It is stated in the Office Action that Figure 8 of Khrapko *et al.* "teaches the use of" a probe array comprising a constant region attached to a solid support (TCGTTTT) and a variable region (the 5' end of the constant region replaced with G, CG or C). It is respectfully submitted, however, that this characterization of Figure 8 is not accurate. First, Khrapko *et al.* does not teach the "use" of anything shown in Figure 8. Rather, as stated in the reference (see page 385, left column), Figure 8 is provided simply to illustrate the effect of mutual stabilization of "side-by-side" duplexes due to a stacking contact between them and the decrease in stability if stacking is disrupted by nucleotide displacement, gap or terminal mismatch. Second, if the sequence TCGTTTT is viewed as a constant region then the only 5' nucleotides of such a sequence shown in Figure 8 are G and C (as shown in sequences 1 and 4 in the figure); there is no CG located 5' of a sequence TCGTTT as stated in the Office Action. Sequence depiction number 2 in the Figure has the following sequence: CGTCGTTT, not CGTCGTTTT as indicated in the Office Action. Even if the construction of Figure 8 proposed in the Office Action is considered, it does not teach or suggest the claimed methods of creating arrays of probes because, as described above, the probes in the arrays created through the claimed methods contain a random sequence within a single-stranded region of the probe. The proposed "variable region" C and G nucleotides 5' of the "constant" region (i.e., TCGTTTT) proposed in the Office Action are **not** within a single-stranded region of the hybrids, and thus the hybrids cannot be manipulated in this way in an attempt to bring them within the probe arrays generated by the claimed methods.

Furthermore, Khrapko *et al.* fails to teach or suggest methods of creating arrays of probes that contain a double-stranded region comprising a constant sequence and a single-stranded region containing a random sequence, as

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specified in claim 1. None of the hybridized matrices described in Khrapko *et al.* contain hybrids in which each hybrid has a common, unvarying, constant sequence found in a double-stranded region of all the hybrids as well as a variable, random sequence within a single-stranded region.

In addition, Khrapko *et al.* fails to teach or suggest methods of creating arrays of probes that contain a double-stranded region and a single-stranded region containing a random sequence of length R, as specified in claims 111 and 113. None of the hybridized matrices described in Khrapko *et al.* contain hybrids which contain varied, random sequences of equal length (i.e., length R) in a single-stranded region.

Drmanac *et al.* does nothing to cure the defects of Khrapko *et al.* As discussed above, in experiments designed to investigate DNA hybridization conditions, individual spots on dot blots (which separately contained a model nucleotide, M13 or an M13 derivative, or unknown clones from a human brain cDNA library in Bluescript vector on apparently different blots) were hybridized with different short oligonucleotides and subjected to conditions designed for increased discrimination of perfectly matched and single-mismatch duplexes. Thus, in some cases, i.e., cases in which the short oligonucleotides were not sufficiently complementary to the target on the dot blot, little to no hybridization was detected. While diminished or lack of hybridization of certain sequences in the dot blots is consistent with the goals that Drmanac *et al.* apparently were attempting to achieve, it in effect teaches away from the claimed methods of creating probe arrays. In the claimed methods, a first set of nucleic acids, each containing a constant and a random sequence, is hybridized with a second set of nucleic acids containing a sequence **complementary** to the constant sequence of the first set of nucleic acids whereby the probes of the resulting array have a double-stranded and single-stranded region. Thus, hybridization and duplex formation between complementary portions of the two sets of nucleic acids are significant elements of the claimed methods of creating an array of probes. In

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contrast, Drmanac *et al.* designed their experimental test hybridizations to be such that hybridization between some of the oligonucleotides and test targets was reduced or eliminated to the point of limited detectability.

It appears that the Office Action relies on Drmanac *et al.* for the proposition of a nucleotide sequence of 11-20 nucleotides with three random positions, and thus allegedly can be used to supply a feature, i.e., variable regions of any size, lacking in Khrapko *et al.*. However, as described above, the defects of the Khrapko *et al.* reference are such that it fails to teach or suggest the claimed methods of creating probe arrays irrespective of how many nucleotides may be contained in a random sequence.

Furthermore, Drmanac *et al.* as an independent reference fails to teach or suggest the claimed methods. Little information is provided in Drmanac *et al.* regarding the exact sequences of any hybrids formed in experiments utilizing M13 and Bluescript vectors as target sequences. In conclusion, there is no teaching or suggestion in Drmanac *et al.* of methods of creating arrays of probes containing a double-stranded region comprising a constant sequence and a single-stranded region containing a random sequence or containing a single-stranded region having a random sequence of length R. Accordingly, the cited art, alone or in combination, fails to result in the claimed methods. It is therefore respectfully submitted that the Office Action fails to establish *prima facie* obviousness of the claimed methods.

The arrays of claims 70-79, 114 and 115 and solid supports of claims 89-94 and 116 are not taught or suggested by the cited references

Claims 70-79, 114 and 115 are directed to an array of nucleic acid probes that have a double-stranded portion and a single-stranded portion containing a random nucleotide sequence. Claims 70-79 and 115 specify that the random nucleotide sequence is of length R. Claim 114 specifies that the double-stranded portion comprises a constant sequence.

Claims 89-94 and 116 are directed to a solid support comprising an array of nucleic acid probes that have a double-stranded portion and a single-stranded

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portion containing a random nucleotide sequence. Claims 89-94 specify that the random nucleotide sequence of the probes is of length R. Claim 116 specifies that the double-stranded portion of the probes comprises a constant sequence.

As discussed above with reference to the rejection of claims directed to methods of creating an array of probes, the experiments described in Khrapko *et al.* and Drmanac *et al.*, alone or in combination, do not teach or suggest arrays of probes that contain a double-stranded region comprising a constant sequence and a single-stranded region containing a random sequence, as specified in claims 114 and 116. Furthermore, Khrapko *et al.* and Drmanac *et al.*, alone or in combination, fail to teach or suggest methods of creating arrays of probes that contain a double-stranded region and a single-stranded region containing a random sequence of length R, as specified in claims 70-79, 89-94 and 115. Accordingly, because the combination of cited references fails to result in the claimed arrays and solid supports, they cannot be relied on to establish *prima facie* obviousness of the claimed compositions.

The methods of claims 95-110 and 117-120 are not taught or suggested by the cited references

Claims 95-110 and 117-120 are directed to methods of sequencing a target nucleic acid including steps of hybridizing target nucleic acid that is at least partly single-stranded to an array of nucleic acid probes that have a double-stranded portion and a single-stranded portion containing a random nucleotide sequence and either detecting the hybridized target nucleic acid for sequencing thereof or determining a hybridization pattern whereby the target nucleic acid is sequenced by analyzing the hybridization pattern. Claims 117 and 119 specify that the random nucleotide sequence is of length R. Claims 118 and 120 specify that the double-stranded portion comprises a constant sequence.

As described above, Khrapko *et al.* describes a technique of sequencing by hybridization with an oligonucleotide matrix which involves hybridization of a

target DNA to be sequenced to single-stranded probes. In contrast, the claimed methods of sequencing a target nucleic acid involve hybridization of an at least partly single-stranded target nucleic acid to an array of nucleic acid probes having a double-stranded portion and a single-stranded portion containing a random sequence. Khrapko *et al.* does not teach or suggest hybridization of target to a probe that has double-stranded and single-stranded portions and a random sequence within the single-stranded portion of the probe.

It is suggested in Khrapko *et al.* that the experiments indicate that additional continuous stacking hybridization (CSH), referred to as hybridization of DNA with immobilized octanucleotides **in the presence of** labeled selected pentanucleotides to form a continuously stacked perfect duplex of 13 base pairs, could increase the fidelity of SHOM (emphasis added, see page 376, first full paragraph in left column). In the description of CSH (p. 385, first full paragraph in left column), Khrapko *et al.* state that it is based on the fact that when two oligonucleotides are **simultaneously** hybridized to a longer one, the two duplexes are mutually stabilized if they are positioned side-by-side due to a stacking contact between them.

Figure 8 of Khrapko *et al.* is said to illustrate this effect. Figure 8 of Khrapko *et al.* does not, however, teach or suggest a nucleic acid sequencing method in which a target to be sequenced is hybridized with probes having double- and single-stranded portions and a random sequence within the single-stranded portion of the probe. Figure 8 shows dissociation curves for four different hybridization products. In the four hybridization reactions, a ³²P-labeled 5-mer and the "test" 17-mer (a model **target** nucleic acid) were **simultaneously** hybridized with an immobilized oligonucleotide (i.e, four different oligonucleotides were immobilized on matrix: 3 different 8-mers and one 7-mer). Thus, just as in SHOM without CSH, when CSH is included in the proposed sequencing method, a target nucleic acid is hybridized with single-stranded probes. At the same time, a labeled pentanucleotide is hybridized to the probe.

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The labeled pentanucleotide is **not** part of the existing collection of probes. This is consistent with the statement in Khrapko *et al.* that CSH is based on the fact that when two oligonucleotides (i.e., the target and the pentanucleotide) are **simultaneously** hybridized to a longer one (i.e., the single-stranded probe), the duplexes are mutually stabilized.

In the sequencing method described in Khrapko *et al.* which involves CSH, apparently because the labeled pentanucleotide is not part of the existing pre-formed probe, a library of labeled 1,024 pentanucleotides is required for CSH (see page 386, upper left column). This method is thus clearly distinct from the methods of sequencing a target nucleic acid as claimed herein. In the claimed methods, the target is hybridized to a preformed array of probes having double- and single-stranded portions and a random sequence within the single-stranded portion. Therefore, Khrapko *et al.* does not teach or suggest the claimed methods of sequencing.

Drmanac *et al.* does not cure the defects of Khrapko *et al.* Drmanac *et al.* does not expressly describe any method for sequencing a target nucleic acid. As indicated by the title of the Drmanac *et al.* reference ("LABORATORY METHODS - Reliable Hybridization of Oligonucleotides as Short as Six Nucleotides"), the reference is directed to experiments designed to identify conditions for reliable hybridization of short oligonucleotides to cloned DNA or oligonucleotides attached to filters. As discussed in detail above, Drmanac *et al.* does not teach or suggest hybridizing target nucleic acids to an array of probes having double- and single-stranded portions and a random sequence in the single-stranded portion. Therefore, the cited art, either alone or in combination, fails to result in the claimed methods for sequencing a target nucleic acid.

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The methods of claims 80-88 and 121-122 are not taught or suggested by the cited references

Claims 80-88 and 121-122 are directed to methods of detecting a target nucleic acid in a biological sample including steps of contacting an array of probes that have a double-stranded portion and a single-stranded portion containing a random nucleotide sequence and identifying hybrids to detect the target nucleic acid. Claim 121 specifies that the random nucleotide sequence is of length R. Claim 122 specifies that the double-stranded portion comprises a constant sequence.

As described above, Khrapko *et al.* describes a technique of sequencing by hybridization with an oligonucleotide matrix which involves hybridization of a target DNA to be sequenced to single-stranded probes. In contrast, the claimed methods of detecting a target nucleic acid involve hybridization of a sample to an array of nucleic acid probes having a double-stranded portion and a single-stranded portion containing a random sequence. Khrapko *et al.* does not teach or suggest hybridization of a nucleic acid to a probe that has double-stranded and single-stranded portions and a random sequence within the single-stranded portion of the probe in any context, and thus does not teach or suggest the claimed methods of detecting a target nucleic acid.

Drmanac *et al.* does not cure the defects of Khrapko *et al.* for the same reason discussed above with respect to other claims. While Drmanac *et al.* may suggest possible applications of their conditions for short oligonucleotide hybridization, it, as well as Khrapko *et al.*, fails to teach or suggest the claimed methods. Therefore, it is respectfully submitted that the Office Action fails to establish *prima facie* obviousness of the claimed methods.


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In view of the above remarks, consideration and allowance of the application is respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Cantor et al.

Serial No.: 09/030,571

Confirmation No.: 7542

Filing Date: February 24, 1998

For: POSITIONAL SEQUENCING BY
HYBRIDIZATION

Art Unit: 1656

Examiner: Houtteman, S.

ATTACHMENT TO THE PRELIMINARY AMENDMENT
MARKED UP AMENDED CLAIMS (37 CFR §1.121)

Please amend claims 1, 3, 4, 70, 71, 80 and 89 as follows:

1. (Twice amended) A method for creating an array of probes, comprising:
 - a) synthesizing a first set of nucleic acids each comprising a constant sequence [of length C at a 3' terminus] and a random sequence [of length R at a 5' terminus];
 - b) synthesizing a second set of nucleic acids each comprising a sequence complementary to the constant sequence of the first nucleic acid; and
 - c) hybridizing the first set of nucleic acids with the second set of nucleic acids, whereby [the step of hybridizing creates the array of probes] the probes in the array have a double-stranded region and a single-stranded region, and
wherein the double-stranded region comprises the constant sequence and the single-stranded region comprises the random sequence.
3. (Amended) The method of claim [1] 113, wherein C is between about 7-20 nucleotides and R is between about 3-5 nucleotides.
4. (Amended) The method of claim [1] 113, wherein the array contains about 4^R different probes.
70. (Amended) An array of nucleic acid probes, wherein each probe has a double-stranded portion, a single stranded portion, and a random nucleotide sequence of length R within the single-stranded portion.

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71. (Amended) The array of claim 70 comprising about 4^R different nucleic acid probes[, wherein R is the length of a random nucleotide sequence within the single-stranded portion of said probe].

80. (Amended) A method for detecting a target nucleic acid in a [biological] sample comprising:

- a) contacting the array of probes with the sample, wherein each probe has a double-stranded portion, a single-stranded portion, and a random sequence within the single-stranded portion; and
- b) identifying hybrids, whereby the target nucleic acid is detected.

89. (Amended) A solid support, comprising an array of nucleic acid probes, wherein each probe has a double-stranded portion, a single-stranded portion, and a random sequence of length R within the single-stranded portion.